PATENT
2039-0124PUS2

IN THE U.S. PATENT AND TRADEMARK OFFICE

APPLICANT:	PRESSATO, D. et al.	CONF:	2626
SERIAL NO.:	10/812,587	GROUP:	1623
FILED:	March 29, 2004	EXAMINER:	MAIER, L.

FOR: BIOMATERIALS FOR PREVENTING POST-SURGICAL ADHESIONS COMPRISED OF HYALURONIC ACID DERIVATIVES

DECLARATION SUBMITTED UNDER 37 C.F.R. § 1.132

Honorable Commissioner
Of Patents and Trademarks
P.O. Box 1450
Alexandria, VA 22313-1450

July 3, 2006

Sir:

I, Dr. Lanfranco Callegaro of Fidia Advanced Biopolymers srl, Italy, do hereby declare the following:

I have attached a copy of my *curriculum vitae* to this Declaration.

I am Chief Executive Officer and Director of Research, and I have worked in this field for 15 years.

I am inventor of the above referenced patent applicatior , and I am familiar with the development, usages and properties of hyaluronic acid and its derivatives.

I have read and understand the subject matter of the Office Action of February 23, 2006.

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The following comments are offered in support of the patentability of the instant invention.

The Examiner has stated that the Malson reference is drawn specifically to hyaluronic acid (HA) that is crosslinked through phosphate ester linkages and that is useful for the applications known for HA *per se* and other crosslinked HA derivatives, such as preventing post-surgical adhesions. She also states that the Malson product is superior because it introduces fewer "alien" products that may result in immunological or inflammatory reactions.

In my opinion, this is not true. The crosslinked HA of the Malson reference is an HA gel derivative which is produced by means of reacting the HA with a phosphorus-containing reagent as crosslinking reagent. This may be phosphorus pentachloride, phosphorus oxychloride or phosphorus pentoxide. Such reagents are, however, highly toxic, as reported in the Merck Index (see attached) where it is clearly stated that they are corrosive on both the mucosa and skin. Moreover, in the attached abstract these substances are used to produce pesticides because they inhibit vital enzymes such as acetylcholinesterase, even at very low concentrations, e.g. those measured in μM.

Example 2 of the Malson reference allows calculation of the quantity of phosphorus oxychloride used to crosslink 300 mg of HA. Here, 400 μl of phosphorus oxychloride is used to crosslink 300 mg of HA. Knowing that $POCl_3$ has a density of d = 1.645 and Mw = 153.33 (Merck Index), since d = m/v, the following calculation can be made: 1.645 = grams/0.4 ml (i.e .400 μl). Thus, 400 μl corresponds to 0.658 grams. Since the Mw is know, the number of moles contained within 400 μl of $POCl_3$ can be calculated as 0.658/1.53.33 = 0.0043 moles. This allows calculation of the molarity of the solution prepared in Example 2 as follows: 0.0043 moles/15 X 1000 = 0.28M. This value of 0.28 M is very high, indeed the attached abstract indicates that concentrations measured in μM are strong enough to be poisonous.

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It is difficult to believe that such an enormous quantity of toxic substance(s) could be completely eliminated without trace amounts present. This is especially so since Example 2 calculates the phosphorus content of the as 0.1%, but the body of the patent states that it is sometimes as high as 1% (see column 4, line 2), which suggests that the values might be influenced by residual crosslinking agent that has not been entirely eliminated. I note that no biological data is presented in the Malson reference, only synthesis. Obviously, any derivative that has the potential to release highly poisonous substances, or degradation products that could react in the physiological environment to produce poisonous substances, could never be used in surgery, let alone to prevent the formation of adhesions.

The Examiner also states that the Malson reference has fewer "alien" products than other known crosslinked HAs. While this may be true, the Malson HA derivatized gel contains phosphorus bridges that crosslink the HA chains. These phosphorus bridges are substances that are foreign to the HA molecule *per se*. On the other hand, the crosslinked HA gel of the instant invention does not contain <u>ar y</u> foreign molecules and degrades without producing any potentially dangerous or reactively dangerous products. This presents an improved result over the Malson reference.

A direct comparison of the Malson product and the HA derivative gel of the application is not practical. Here, *in vivo* tests would be necessary using live animal models. It is extremely difficult to obtain approval for tests that are known to inflict pain and suffering on animals. In this case, because of the high potential for toxicity from use of the Malson product, it would be difficult to ethically conduct such comparative tests.

To summarize, in my opinion the Examiner is incorrect to think that any HA derivative can be substituted for any other, that the Malson derivative is without foreign substances and that its crosslinking is similar to that of the derivatives described in the invention.

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The undersigned hereby declares that all statements made herein based upon knowledge are true, and that all statements made based upon information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

DATED: 07/11/2006

Dr. Lanfranco Callegaro

CURRICULUM VITAE
LANFRANCO CALLEGARO

PERSONAL PARTICULARS:

Name:	Lanfranco Callegaro
Date & Place of Birth:	23/06/1951 – Noventa Padovana (PD), Italy
Marital Status:	Married; 2 children
Citizenship:	Italian

EDUCATION:

1970	Graduated from High School
1975	Degree in Chemical Sciences, University of Padua

PRESENT POSITION:

2001 – present	Chief Operating Officer, Fidia Farmaceutici SpA
1994 – present	Chief Executive Officer, Fidia Advanced Biopolymers Srl

PROFESSIONAL APPOINTMENTS:

1976 – 1979	Postdoctoral Fellow, Protein Chemistry, Biopolymers Center, national Research Council, University of Padua
1979 – 1984	Senior Researcher, Biomedical Department, Sorin Biomedica, Saluggia (VC), Italy
1984 – 1986	Director, Immunodiagnostic Research and Development, Sorin Biomedica, Saluggia (VC), Italy
1986 – 1989	Chief, Molecular Biochemistry Department, Fidia SpA, Abano Terme (PD), Italy
1992 – 1994	Founder and Managing Director, Fidia Advanced Biopolymers Srl (Fidia Group), Abano Terme (PD), Italy
1994 – 2001	Director, Corporate Development, Fidia SpA, Abano Terme (PD), Italy

MAJOR INDUSTRIAL PERFORMANCES

Development at Sorin Biomedica SpA of a number of radioactive products using monoclonal antibodies for the detection in vivo of tumoral massess.
Development of diagnostic tests for the hepatitis, HIV and tumora markers determination.

Founder of the biotech company, Fidia Advanced Biopolymers (FAB) which is focused on the development, production and commercialization of Tissue Engineered products and innovative biomaterials for surgical applications, I enhanced the internationalization of R&D and industrial activities, the partecipation and the coordination of European Projects in Tissue Engineering and industrial technologies areas.

As far as Fidia farmaceutici is concerned:
Internationalization of the main products.
Coordinator of Strategic R&D and Industrial Development Projects.
Reorganization of the Italian products list and of the national sales force.
Organization of national and international regulatory activities and Delegation owner for the relations with the national and international Authorities.